# Usefulness of Endomyocardial Biopsy in Tertiary Care

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*Over a 51-month period, 143 patients underwent right ventricular endomyocardial biopsy as part of their evaluation for cardiac disease. Of these, 82 patients presented with a clinical dilated cardiomyopathy, 28 patients with unexplained arrhythmia, 22 with other cardiomyopathies, 7 with anthracycline exposure, and 4 with miscellaneous indications. Overall, 47 of the 143 patients (33%) had findings on endomyocardial biopsy that changed the clinical diagnosis. Of these, 18 (38%) had a change in diagnosis based on nonspecific criteria. Although 32 of the 143 patients (22%) had specific therapeutic alterations based on the endomyocardial biopsy findings, the vast majority of these received immunosuppression for myocarditis, a therapy that is currently of unproven benefit. Therefore, endomyocardial biopsy is of limited therapeutic use for most patients with primary myocardial disease. Its current primary indications are for clinical diagnosis and investigation.*

(Hosenpud JD: Usefulness of endomyocardial biopsy in tertiary care. West J Med 1989 Jan; 150:43-45)

Endomyocardial biopsy has been reported as an aid to the diagnosis of several disease states involving the myocardium.[1] A diagnostic study should, however, either provide new information or its results should somehow influence therapeutic decisions, or both. An endomyocardial biopsy is an invasive procedure that is costly and not without risk.[2] Its overall usefulness in providing the above-stated goals has rarely been rigorously analyzed.[3] Accordingly, the records of all patients undergoing endomyocardial biopsy for various indications (excluding cardiac transplant follow-up) were analyzed retrospectively to determine whether the results of the procedure influenced subsequent care.

## Patients and Methods

The records of all patients undergoing an endomyocardial biopsy from September 1982 to February 1987 were reviewed. If a patient had more than one biopsy for follow-up of a specific disease, only the first biopsy done for an initial diagnosis was used in the analysis. A specific indication category was chosen at the time of the biopsy procedure in all instances and noted on the request for pathologic evaluation. This indication category also determined the quantity of tissue taken, the fixative used, and the specific stains required, if any. The specific indication categories were dilated cardiomyopathy (rule out myocarditis); hypertrophic cardiomyopathy; restrictive cardiomyopathy; indeterminate cardiomyopathy (unable to classify); unexplained arrhythmia (no obvious structural heart disease); anthracycline therapy; and other, where specific indications not falling into other categories were noted.

Following receipt of the final pathologic interpretation, the medical record was reviewed and the following additional data were acquired: duration of and specific symptoms, physical findings, medications, laboratory studies including invasive and noninvasive cardiac function studies if done, final diagnosis, and the presence of a therapeutic manipulation based on biopsy findings.

The final pathologic report was used for data analysis. All endomyocardial biopsies were evaluated for the presence of inflammation, necrosis, hypertrophy, fibrosis, and myocardial cell nuclear atypia. In addition, abnormalities such as amyloid deposition were noted if specific stains were indicated by the clinical presentation. Cardiomyopathic changes were considered present when fibrosis, hypertrophy, and nuclear atypia were noted.[4] A diagnosis of chronic lymphocytic myocarditis was made if both lymphocytic infiltrate and myocardial cell necrosis were present, based on long-standing criteria of this institution and as more recently suggested by Aretz and colleagues.[5] A specific number of lymphocytes per area of myocardium was not used in making the diagnosis of myocarditis. Myocardial damage due to anthracycline toxicity (intracellular vacuolization and myofibrillar loss) was graded from 0 to 3 based on criteria developed by Billingham and co-workers.[6] Other specific disease processes were based on standard pathologic criteria.

The specific indications, clinical characteristics, pathologic diagnosis, final diagnosis, and specific therapy, if any, were then analyzed. A change in clinical diagnosis would include the following: myocarditis in a patient with dilated cardiomyopathy, cardiomyopathy in a patient with unexplained arrhythmias, amyloidosis or other specific disease process in a patient with a nonetiologic diagnosis such as restrictive or hypertrophic cardiomyopathy. Biopsy-directed therapy would include the following: immunosuppression for myocardial inflammation; alteration in the anthracycline dose based on biopsy findings; exclusion from other therapies because of biopsy findings, such as excluding from heart transplantation or a more extensive evaluation because of amyloid deposition in the myocardium.

Statistical differences between groups of patients were

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determined using Student's *t* test for nonpaired data and Fisher's exact test where appropriate. Significance was considered present at a *P* value of less than .05.

## Results

During the study period, 143 patients underwent an endomyocardial biopsy using the Caves-Schultz bioptome. Their ages ranged from 12 to 72 years (mean 43 years), and symptom duration ranged from 1 day to 312 months (mean 23 months). Although 19 patients underwent more than one biopsy for follow-up of their specific disease process, only the first biopsy from these patients was used in this analysis. Table 1 shows the number of patients and percentage of the group undergoing biopsy for each specific indication. The two most common indications at this institution were clinically dilated cardiomyopathy of unknown etiology and unexplained arrhythmia. Complications related to the endomyocardial biopsy were few and included myocardial perforation (3%), pneumothorax, asymptomatic air embolism, and supraventricular arrhythmias (each 1%). Nearly all of the complications occurred in the first 25 procedures done, consistent with a learning curve, and there were no deaths related to the procedure.

Table 2 shows the pathologic diagnoses made by biopsy for the entire group. The most frequent diagnosis was cardiomyopathy, with myocarditis the second most frequent. Only 16 patients had completely normal results.

Of the 82 patients who presented with a clinically dilated cardiomyopathy, 22 showed histologic evidence of myocardial inflammation (chronic lymphocytic myocarditis). Figure 1 summarizes the clinical and hemodynamic findings of patients with dilated cardiomyopathy with and without myocardial inflammation. In this series, patients with myocarditis were significantly younger, had a shorter symptom duration, and had a more equal male-to-female incidence compared with those with dilated cardiomyopathy. Also, the mean heart rate was significantly faster and left ventricular chamber size smaller in those with myocarditis on biopsy.

Table 3 summarizes those cases in which, as a result of the endomyocardial biopsy, the diagnosis was changed. In all, 47 new diagnoses were made by endomyocardial biopsy.

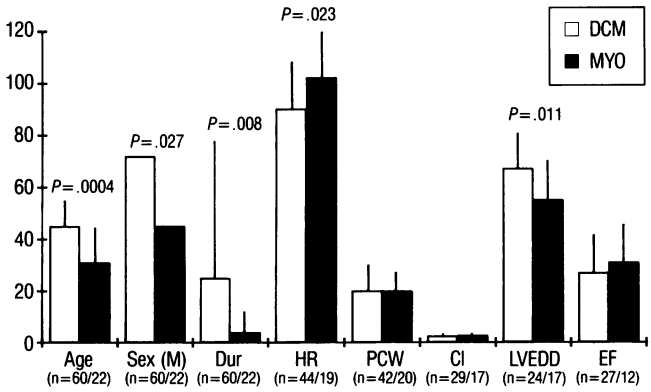


**Figure 1.**—The graph shows clinical and hemodynamic variables in patients with dilated cardiomyopathy (DCM; white bars) and myocarditis (MYO; black bars). Sex (M) = percentage of male patients, Dur = symptom duration in months, HR = heart rate (beats per minute), PCW = pulmonary wedge pressure (mm of mercury), CI = cardiac index (liters/min/m$^2$), LVEDD = echo left ventricular end-diastolic dimension (mm), EF = ejection fraction (%), n = cohort size for DCM/MYO for each variable measured. Results are expressed as mean ± 1 standard deviation.

Included in this total were 18 patients with unexplained arrhythmias who had changes consistent with but not diagnostic of cardiomyopathy. In support of a diffuse myocardial process in these 18 patients was their reduced ejection fractions (0.54 ± 0.20) and elevated pulmonary wedge pressures (14 ± 10 mm of mercury).

Table 4 summarizes those cases in which, as a result of the biopsy, there was a change in therapy. As shown, 32 patients underwent specific changes in their therapeutic regimen based on the results of the endocardial biopsy. Of these 32 patients, 24 received immunosuppression for a biopsy diagnosis of myocarditis, a currently unproven mode of

TABLE 1.—*Indications for Endomyocardial Biopsy*

| Indication | Patients Number | Patients Percent |
|---|---|---|
| Dilated cardiomyopathy | 82 | 57 |
| Unexplained arrhythmia | 28 | 20 |
| Restrictive cardiomyopathy | 9 | 6 |
| Indeterminate cardiomyopathy | 8 | 6 |
| Anthracycline therapy | 7 | 5 |
| Hypertrophic cardiomyopathy | 5 | 3 |
| Other | 4 | 3 |
| Total | 143 | 100 |

TABLE 2.—*Pathologic Diagnoses From Myocardial Biopsy*

| Diagnosis | Patients Number | Patients Percent |
|---|---|---|
| Cardiomyopathy | 90 | 63 |
| Lymphocytic myocarditis | 24 | 17 |
| Giant cell myocarditis | 2 | 1 |
| Anthracycline toxicity | 4 | 3 |
| Amyloidosis | 2 | 1 |
| Vasculitis | 1 | 1 |
| Normal histology | 16 | 11 |
| Indeterminate or inadequate | 4 | 3 |
| Total | 143 | 100 |

TABLE 3.—*Patients in Whom Biopsy Findings Altered Diagnosis*

| Clinical Diagnosis | Biopsy Diagnosis | Patients, Number |
|---|---|---|
| Dilated cardiomyopathy | | 82 |
| | Myocarditis | 22 |
| Unexplained arrhythmia | | 28 |
| | Cardiomyopathy | 18 |
| | Myocarditis | 2 |
| | Granulomatous myocarditis | 2 |
| | Arteritis | 1 |
| Restrictive cardiomyopathy | | 9 |
| | Amyloidosis | 2 |

TABLE 4.—*Patients in Whom Biopsy Findings Altered Treatment*

| Biopsy Diagnosis | Therapeutic Intervention | Patients, Number |
|---|---|---|
| Myocarditis | Azathioprine and prednisone | 22 |
| Granulomatous myocarditis | Prednisone | 2 |
| Anthracycline toxicity | Alteration of dose | 7 |
| Amyloidosis | No heart transplant | 1 |

therapy. Eliminating these patients would leave a total of only eight patients who had a clinically justifiable change in therapy. Seven of these eight underwent a biopsy specifically for a therapeutic decision (anthracycline therapy). The other patient was referred for cardiac transplantation with a "hypertrophic" cardiomyopathy. Amyloidosis was unexpectedly discovered on endomyocardial biopsy, and the patient was therefore felt not to be a candidate for transplantation.

## Discussion

Transvenous endomyocardial biopsy was first reported by Sakakibara and Konno in 1962.[7] Its use as a routine cardiologic diagnostic tool was limited, however, until the early 1970s when endomyocardial biopsy became the method of choice for following cases of cardiac allograft rejection.[8] It was not until after 1980, in response to a report by Mason and associates,[9] that endomyocardial biopsy gained favor for evaluating primary myocardial disease. The specific use was in patients with dilated cardiomyopathy to rule out myocarditis. It has also been used to evaluate anthracycline toxicity,[6] to define other forms of cardiomyopathy,[10,11] and to evaluate patients with unexplained arrhythmias, of whom a high percentage will have unexpected pathologic disease.[12-14] Several reviews of the procedure outline the diagnoses that can and have been made using endomyocardial biopsy.[1,15,16] Only rarely have these reports specifically determined the incidence of diagnostic findings, even less often the impact of the diagnostic findings on patient care.[3]

A recent editorial by Mason suggests that the role of endomyocardial biopsy will be limited to searching for "needles in a haystack."[17] The current analytic study supports these conclusions. Although 33% of the patients had a biopsy-caused change in diagnosis, of this subgroup, more than a third—those with arrhythmia as an indication—had the diagnosis of cardiomyopathy made on the basis of fairly nonspecific histologic findings,[4] and their presence in the general population is unknown. The findings of reduced ejection fractions and elevated filling pressures in this subgroup support the diagnosis and may have prognostic implications.

The other large group in whom a biopsy changed the diagnosis were those with myocarditis. This is likely a legitimate diagnostic category, as the prognosis in these patients may differ considerably from that in patients without myocardial inflammation.[18] As can be seen by the clinical characteristics between those with and without inflammation, the diagnosis must be made histologically. The benefit of a specific intervention for myocarditis is still unproved,[19] and the diagnostic criteria used in making a diagnosis of myocarditis are open to debate even among experienced pathologists.[5,20,21]

What, then, are firm indications for an endomyocardial biopsy? The least controversial indication not addressed in this series is to diagnose rejection in a cardiac allograft.[8] Other well-documented indications include monitoring for anthracycline cardiac toxicity[6] and the diagnosis of specific although uncommon myocardial or systemic diseases such as amyloidosis, hemochromatosis, and sarcoidosis.[10,22,23]

A less firm indication is for those patients with a recently occurring dilated cardiomyopathy to rule out myocarditis. This approach may be justifiable from a prognostic standpoint,[18] although this is controversial.[24] In addition, there are data from studies in animals to suggest that exercise during active myocardial inflammation may exacerbate myocardial dysfunction.[25,26] It is hoped that specific therapy will ultimately be available for myocarditis, further justifying the need for a specific diagnosis.

Finally, there appears to be a high incidence of unsuspected myocardial disease in patients with normal cardiac function and unexplained arrhythmias.[12-14] Although, again, in most cases specific therapy is not available, there may be important prognostic implications to the biopsy findings.

If therapeutic intervention is the only justification for a diagnostic procedure, then endomyocardial biopsy today has relatively few absolute indications. Endomyocardial biopsy, however, has provided and, it is hoped, will continue to provide new information for better understanding and classification of primary myocardial diseases. This must occur before a specific therapy can be forthcoming.

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